EUROPEAN COMMISSION
JOINT RESEARCH CENTRE

Institute for Health and Consumer Protection
In vitro methods Unit
European Centre for the Validation of Alternative Methods (ECVAM)

STATEMENT ON

THE USE OF EXISTING LOW VOLUME EYE TEST (LVET) DATA FOR WEIGHT OF EVICENCE DECISIONS ON CLASSIFICATION AND LABELLING OF CLEANING PRODUCTS AND THEIR MAIN INGREDIENTS

At its 31st meeting, held on 7 and 8 July 2009, the non-Commission members of the ECVAM Scientific Advisory Committee (ESAC) unanimously endorsed the following statement:

1. The ESAC strongly recommends that the Low Volume Eye Test (LVET) method, a modification of the standard Draize eye test, is NOT conducted in the future to generate new testing data concerning the intrinsic properties of xenobiotic substances (chemicals, cosmetic ingredients etc.).

2. ESAC nevertheless acknowledges that existing[1] LVET data of the limited use domain of household detergents and cleaning products as well as their main ingredient class (i.e. surfactants as used in these products) may be used for purposes of classification and labelling decisions.

3. Moreover, existing LVET data of this limited use domain may be used as supplementary data in the context of a subset of future validation studies.

4. Finally, the ESAC recommends that no additional testing is done to further develop or validate the LVET test method.

The ESAC recommends that consideration be given on a case by case basis to the limited use of existing Low Volume Eye Test (LVET) data as supplementary in vivo data within Weight of Evidence (WoE) evaluations of alternative testing methods and strategies, and for decision making on the necessity to conduct additional standard in vivo test method(s) for eye irritation for purposes of classification and labelling for the above specified limited use domain.

This recommendation is based on conclusions reached following the assessment of a dossier submitted to ECVAM concerning data and test results relating to detergents, cleaning products and, to a lesser extent, their main ingredients (surfactants).

In making these recommendations, ESAC acknowledges:

(1) the considerable amount of existing LVET data for the domain of household detergents and cleaning products;

(2) that the LVET makes use of direct corneal exposure to mimic specific human exposure scenarios that can be reasonably expected (e.g. accidental ocular exposure during household use) and for the specific use domain of household detergents and cleaning products as well as their main ingredients (i.e. surfactants) as used in these products.

[1] Existing data in this context refers to data that were generated ***prior*** to the date of this statement.

(3) that LVET data, being based on exposure scenarios likely to be relevant in humans, may predict effects in humans with improved accuracy when compared to the Conventional Calculation Method (CCM) traditionally used for C&L decisions on products of this use domain;

(4) the provisions of the Regulation on the Classification, Labelling and Packaging of Substances and Mixtures ('CLP' Regulation 1272/2008/EC; Ref. 1), which foresees an WoE assessment based on existing data to determine whether or not testing with accepted standard tests (i.e. those described in the Test Method Regulation 440/2008/EC; Ref. 2) is necessary or may be dispensed with.

The ESAC furthermore recognises that several databases for alternative methods for eye irritation test methods may be of an acceptable size only if existing LVET testing data can be considered as an additional and secondary source of supporting information. Some differences in classification based on LVET data are to be expected with respect to reference data for the established eye irritation test (i.e. Draize eye data), and the tendency of them to give lower hazard categories than the classical Draize eye test (Ref. 3) must be kept in mind. Nevertheless these data may still be useful on a case by case basis, and only with respect to testing data for household detergents, cleaning products and surfactants used in such products. Subject to these considerations existing LVET data may on occasion contribute to a knowledge base against which alternative methods may be validated for this specific use domain.

Joachim Kreysa

Head of Unit

In-Vitro Methods Unit

European Centre for the Validation of Alternative Methods

Ispra, 9. July 2009

Explanatory background to this ESAC recommendation:

This recommendation is based on a submission of LVET data to ECVAM concerning household detergents and cleaning products as well as their main ingredient class, i.e. surfactants. The LVET data were correlated to effects in man observed in response to accidental splashes and as documented in poison control centres and clinics. To a lesser extent also clinical exposure data from human volunteers on substances of the mild irritant range were used. The submission was evaluated by ECVAM in 2006 and, after requested amendments had been performed, underwent independent ESAC peer review from April 2007 to June 2009.

The LVET is a minor modification of the classical Draize eye irritation test (Ref. 4): the LVET differs from the Draize test only with regard to two aspects both relating to exposure: (1) The LVET uses only a tenth of the volume of liquids (=10µL) or weight of solids (=10mg) in comparison to the Drazie (0.1 mL of liquids and 100mg of solids); (2) both liquids and solids are applied directly on the cornea in the LVET, without subsequent forced closure of eyelids, in contrast to the Draize test where the test material is instilled in the conjunctival sac of the rabbit eye. All other parameters such as e.g. exposure time and visual scoring of effects on the cornea, conjunctiva and iris are unchanged with regard to the Draize eye test. All other parameters such as e.g. exposure time and visual scoring of effects on the cornea, conjunctiva and iris are unchanged with regard to the Draize test. The rationale for using a reduced amount of test substances (as described in the submission) and for applying it directly to the cornea is to mimick household exposure scenarios such as accidental splashes with detergents and cleaning products in man and to consequently approximate the effects in man. The ESAC PRP held that while such exposure scenarios may be reasonable specifically for household detergents and cleaning products they do not take into consideration other possible routes of exposure such as, for instance, the accidental exposure to pesticides using pressure pumps during field work. Thus, while the LVET exposure settings may be appropriate for household exposure to cleaning products and, possibly, personal hygiene products (i.e. cosmetics), they do at present not appear appropriate for a wide range of substances and associated exposure scenarios – at least until further data supporting such use becomes available.

The LVET has been and is used mainly by industry to benchmark finished products (formulations = mixtures= preparations), a blend of individual chemical substances purposefully mixed in measured and defined proportions for specific uses and applications (e.g. cleaning products, shampoos etc.). In practice, LVET data were used to contribute to classification and labelling decisions. Up to January 2009, when the new CLP regulation came into force (see below), classification and labelling of substances was performed according to the Dangerous Substance Directive (Directive 67/548/EEC; Ref. 5) and that of mixtures according to the Dangerous Preparations Directive (Directive 1999/45/EC; Ref. 6). In December 2008 the EU adopted the Regulation on the Classification, Labelling and Packaging of Substances and Mixtures (so-called CLP regulation 1272/2008/EC; Ref. 1) that aligns existing EU legislation to the United Nations Globally Harmonised System (GHS). The CLP Regulation will, after a transitional period, replace the current rules on classification, labelling and packaging of substances (Directive 67/548/EEC; Ref. 5) and mixtures (Directive 1999/45/EC; Ref. 6). The date from which classification and labelling must be consistent with the new rules will be 1 December 2010 for substances and 1 June 2015 for mixtures. Notably,

the CLP regulation amends the REACH regulation (concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals, 'REACH'; 1907/2006/EC, Ref. 7) with respect to classification and labelling.

Both, the CLP regulation and REACH foresee the possibility of WoE assessments to decide on the necessity of standard tests to be performed (i.e. tests laid down in the Test Method Regulation 440/2008/EC; Ref. 2): the CLP regulation in the context of classification and labelling decisions of substances and mixtures (formerly referred to as 'preparations' or 'formulations'; these may include finished products for consumer use) and REACH in the context of chemical safety assessments.

WoE approaches are based on the integration of data from various sources and make use of synergistic effects obtained by combining data sets in cases where each single data on its own would be insufficient for decision-making but where the combination of data may allow conclusions on the absence or presence of dangerous properties of substances as regulated by the CLP regulation and the REACH regulation and finished products (i.e. "mixtures", previously referred to as "preparations"), as regulated by the CLP regulation.

LVET data related to above mentioned use domain may be helpful, together with other existing and available data from various sources, to decide in a WoE approach in the contexts of the two above mentioned regulations whether confirmatory standard test(s) for eye irritation are necessary or whether existing information, in its totality, is sufficient to arrive at classification and labelling conclusions without performing further testing of the substance/product in question.

In summary the ESAC recommendation takes into consideration:

(a) the non-negligible amount of human reference data collected in the submitted dossier;

(b) the fact that LVET data, as the classical Draize eye test, reflect these human exposure data at least for above mentioned and limited use domain (e.g. detergents/cleaning products and surfactants) (see however point c)

(c) the fact that most of the exposed patients had received anti-inflammatory treatment which complicates an appraisal to which extent observed effect in patients represented the actual hazard to be expected under observation of the precautionary principle;

(d) the appraisal that the exposure settings of the LVET may represent the exposure from accidental splashes more appropriately than the classical Draize eye test;

(e) the common practices concerning the labelling of finished products under the Dangerous Preparations Directive (Ref. 6) as well as the future practice using WoE evaluations for substance and product classification and labelling as outlined in the CLP regulation (Ref. 1);

(f) the fact that the LVET is only a very minor variation of the Draize test with no impact on i) the amount of animals required for testing and ii) with unknown effects for the test animals with regard to the extent of stress and suffering inflicted.

(g) the potential usefulness of existing LVET data as reference data for validation purposes of alternative methods to assess the ocular irritancy potential of raw materials (surfactants) and finished products of the use domain of detergents and cleaning products.

(h) the comparable reproducibility of the LVET when compared to he Draize eye test.

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The ESAC was established by the European Commission, and is composed of nominees from the EU Member States, industry, academia and animal welfare organisations, together with representatives of the relevant Commission services.

This statement was endorsed by the following members of the ESAC:

Ms Argelia Castaño(Spain)
Ms Maija Dambrova (Latvia)
Ms Alison Gray (ESTIV)
Ms Katalin Horvath (Hungary)
Ms Dagmar Jírová (Czech Republic)
Mr Roman Kolar (Eurogroup for Animals)
Ms Elisabeth Knudsen (Denmark - acting as moderator at the meeting)
Mr Manfred Liebsch (Germany)
Mr Gianni Dal Negro (EFPIA)
Mr. Walter Pfaller (Austria)
Mr Tõnu Püssa (Estonia)
Mr Dariusz Sladowski (Poland)
Mr Jon Richmond (UK)
Ms Vera Rogiers (ECOPA)
Mr Michael Ryan (Ireland)
Ms Annalaura Stammati (Italy)
Mr Jan van der Valk (The Netherlands)
Mr Carl Westmoreland (COLIPA)
Mr Timo Ylikomi (Finland)

The following Commission Services and Observer Organisations were involved in the consultation process, but not in the endorsement process itself:

Commission services
Mr Joachim Kreysa (DG JRC, Head of In vitro methods Unit/ECVAM, chairman)
Mr Claudius Griesinger (DG JRC, ESAC secretariat)
Ms Susanne Hoke (DG ENTR)
Ms Susanna Louhimies (DG ENV)
Mr Juan Riego Sintes (DG JRC)

The following observers were present
Mr Hajime Kojima (JaCVAM)
Mr William Stokes (NICEATM)
Ms Marilyn Wind (ICCVAM)